Remarks

Claims 49 and 54 have been amended to indicate equivalence of the lower molecular weight form of GAD with GAD65. These alternate terminologies are interchangeably in the specification (see, e.g., p. 36, lines 27-29) Support for new claim 58 and 59 is provided at e.g., p. 11, line 6.

The paragraph numbering of the office action is used in responding to the Examiner's comments.

6-13. Claims 31, 34, and 35 stand rejected for alleged lack of enablement for the same reasons set forth in the previous office action. In response, Applicants draw the Examiner attention to the inconsistency between the maintenance of the rejection in the present application, and the issuance or indication of allowability of substantially similar claims in two other patent filings having priority dates approximately contemporaneous with that of the present application. These filings are Atkinson, US 5,762,937 (of record) and Tobin, USSN 08/485,725 (owned by the University of California, a co-assignee of the present application). Papers from the '725 file history showing claims indicated allowable and an indication of allowability subject to interference (presumably with the '937 patent) are attached. The present specification provides at least as much guidance as the '937 patent regarding the use of GAD as a therapeutic reagent. In these circumstances, it is apparent that the PTO is applying an inconsistent standard of enablement in examining the present application. Not only is this inequitable to the present applicants, but it creates a risk of wasting judicial resources in allowing an interference to be conducted between only two of three filings, all with similar disclosures and priority dates. For these reasons, it is submitted that the enablement rejection should be withdrawn and the present application included in an interference with the '937 patent and the '725 application. A formal request for an interference will be made on indication of otherwise allowable subject matter.

The inconsistent treatment of the present application vis-a-vis the '937 patent and '725 application appears to arise due to an unduly high standard of enablement being applied in the present case. As was noted in the last response, the utility requirement of 35 USC 101 is generally satisfied by evidence of a pharmacological activity in a laboratory animal. Further, requests by office personnel for of safety in treatment of humans or regarding

degree of effectiveness are improper (MPEP $2107). It is acknowledged that the present rejection is brought under 35 USC 112, first paragraph rather than 35 USC 101. Nevertheless, insofar as the rejection is directed to the alleged inoperability of the invention, the same standard applies under either statute. Such is clear from the *In re Brana* 34 U.S.P.Q.2d 1436 case (No. 93-1393 Fed. Cir. 1995), in which the Federal Circuit considered a rejection for lack of utility brought under §112, first paragraph. In finding that the PTO had acted arbitrary and capriciously in denying patentability on the basis of mouse data, the Federal Circuit cited several cases under §101 as authority for its decision. Such is also clear from the *Guidelines for Examination of Applications for Compliance with the Utility Requirement*:

> A §112, first paragraph, rejection [based on lack of utility] should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under §101 under these guidelines.

Legal Analysis Supporting Utility Examination Guidelines at §I.D MPEP §2107.

Under the appropriate standard of inquiry, it is maintained that the rejection under 35 USC 112, first paragraph should be withdrawn for the reasons indicated in the last response. The Examiner's additional comments in the present office action will now be briefly addressed in turn.

First, the Examiner cites Tisch as disclosing that a key question is whether administration of autoantigen can treat ongoing disease or whether it is useful only in preventing disease. The Examiner then faults applicants for failing to "disclose a method of treating using GAD that would actually prevent the onset of IDDM" (office action at paragraph (9)). The Examiner's criticism appears directly contrary to Tisch's comment, in that Tisch apparently considers that prevention of onset to be more likely to be achieved than treatment of ongoing disease. In any event, the underlying issue raised by the Examiner is one of the degree of effectiveness of the claimed methods and compositions in treatment. As previously indicated, such an inquiry is explicitly prohibited under 35 USC 101. Further, when issues of operability that could be raised under 35 USC 101 are raised under 35 USC 112, first paragraph, the same standard applies.

Second, the Examiner criticizes the application for not disclosing dosages or route of administration (office action at paragraph (9)). However, the Examiner has

overlooked the guidance that has been provided as to both dosage and route of administration at pp. 20-21 of the specification. Specifically, the application identifies a typical range of dosages of about 1 to 500 mg GAD per kg body weight with a preferred range of about 5 to 25 mg/kg body weight. The application also refers to parental administration and, in particular, to intravenous administration. It is noted that dosage of the order of 100 micrograms to 2 mg per mouse have proved successful in tolerization of mice (see Elliot, *Diabetes* 43, 1494-1499 (1994) and Petersen, *Diabetes* 44, 1478-1484 (1994)). Taking into account the different mass of mice and humans, these dosages are certainly within the order of magnitude contemplated by applicants. Further, Harrison, *Molecular Medicine* 1, 722-727 (1995) (of record) at p. 724, column 1 reports that at least three parenteral routes of administration, including intravenous administration of GAD delay the onset or reduce the incidence of IDDM. Furthermore, the '937 patent provides less guidance on dosage and route of administration than the present application, highlighting the unduly high standard of enablement by which the present application is being examined.

Next, the Examiner questions whether the GAD referred to in the present claims is the same GAD used by Tisch et al. (BO), Kaufman (BG), or Peterson et al. (W2) (office action at paragraph (10)). This issue is apparently raised because of the specification's reference to a 64 kDa pancreatic autoantigen whereas the cited references refer to GAD65. In response, the Examiner is advised that there are only two known forms of GAD, conventionally referred to as lower molecular weight GAD (GAD65) and higher molecular weight GAD (GAD67) (see e.g., Erlander et al., *Neuron* 7, 91-100 (1991), Bu et al., *Proc. Natl. Acad. Sci.* USA 89, 2115-2119 (1992)). It is generally recognized in the art that GAD65 is equivalent of the pancreatic 64 kDa autoantigen (see e.g., Tobin, US 5,674,978 (of record) at col. 26, lines 65-66 ("GAD65, previously known as the 64K autoantigen"). Moreover, in addition to the reference to the pancreatic 64 kDa autoantigen, the present specification does explicitly refer to lower and higher molecular weight forms of GAD as GAD65 and GAD67 respectively (see, e.g., p. 36, lines 27-29).. Thus, it is submitted to be clear that applicants are referring to the same GAD as discussed in the same cited references (and in the '937 patent).

Next, the Examiner repeats previous comments regarding possible difficulties resulting from the existence of multiple autoantigens in diseases such as IDDM. However, the

Examiner does not address applicants response to this point (paragraph bridging pp. 5-6 of response of October 28, 1998). To recap, it has been reported that a T-cell response to GAD65 develops early in development of IDDM and subsequently spreads to other β-cell antigens in a cascade of responses that ultimately lead to IDDM (see Tian et al., *Nature Medicine* 12, 1348 (1996), column 1, first paragraph). Thus, it would be expected that inducing tolerance to GAD65 would abort subsequent events in the cascade of events leading to IDDM. This expectation is supported by the several publications reporting that GAD65 or peptides thereof inhibit development of IDDM in laboratory animals (see e.g., Tisch et al. (BO), Kaufman (BG), Tian et al., *supra*, Peterson et al., *Diabetes* 44, 1478 (1994), and Pleau et al., *J. Immunol. Immunopath.* 76, 90-95 (1995)). Moreover, it is noted that the difficulties alleged by the Examiner would apply equally to the issued claims in the '937 patent, further highlighting the inconsistency in treatment of the present application.

Next, the Examiner reiterates a specific phrase in the Lernmark reference stating that other investigators have not found published procedures to be easily reproducible (office action at paragraph (11)). Applicants response is that the Examiner is giving undue emphasis to a brief and passing comment at the expense of the totality of numerous publications in peer-reviewed journals already of record indicating that GAD shows a pharmacological activity in treatment of IDDM in animal models. The only reference cited by Lernmark in the excerpt referred to by the Examiner is Petersen, *Diabetes* 44, 1478-1484 (1994) (of record). However, this reference provides evidence that GAD can be successfully used to delay the onset of diabetes in neonatal NOD mice, and thus supports rather than contradicts enablement of the present claims. Again, it is noted that if this basis of rejection did have any validity, it would be equally applicable to the Atkinson '937 patent

Next, the Examiner says that she is not requiring evidence of lack of toxicity in humans but that lack of toxicity is inherent in treatment (office action at paragraph (12)). The Examiner says that applicant has provided only *in vitro* experiments to "demonstrate operability of the claimed polypeptide" (office action at paragraph (12)). The Examiner's explicit use of the term "operability" confirms that alleged lack of operability is the underlying basis of the rejection. As previously stated, whether operability is considered under 101 or 35 USC 112, first paragraph, the standard is the same. Here, applicants have not only provided *in*

vitro evidence, but have cited numerous publications indicating a pharmacological activity of GAD in animal models of diabetes. Such is sufficient to establish operability. Further, it is noted that any allegations of lack of inoperability toward the present claims are at least equally applicable to the '937 patent. For the reasons advanced above, it is submitted to be imperative that a uniform standard is applied.

Finally, the Examiner suggests that applicants submit evidence in support of that fact that administration of GAD ameliorates diabetes phenomena and suggests Elliott et al., *Diabetes* 43, 1494 (1994) and Peterson, *Diabetes* 44, 1478 (1994) as suitable references. In fact, the Peterson reference was already submitted together with other references as evidence that GAD ameliorates diabetes phenomenon (see response of October 28, 1998 at p. 6, first paragraph). Applicants agree that the Elliot reference provides still further evidence of such a role for GAD, and attach it with the present response.

17. Claim 31 stands rejected under 35 USC 102(a) as being anticipated by Atkinson, US 5,762,937. It is assumed that the rejection was intended to be under 35 USC 102(e) because the '937 patent published long after the priority date of the present application and is not 35 USC 102(a) prior art with respect to it. Applicants request that the issue under 102(e) be resolved by interference. A formal request for an interference will made on indication of otherwise allowable subject matter.

19-22. Claims 49-53 added with the last response are subject to essentially the same rejection under 35 USC 112, first paragraph as other claims. Applicants respond as above. Claim 34 is rejected on additional grounds for referring to fragments of GAD. Such reference has been deleted to moot the rejection.

24. It is believed that the subject matter of all claims was commonly owned by the University of California and Yale University at the date of invention.

26. Claims 35 and 54-57 stand rejected as obvious over Chang & Gottlieb. The Examiner acknowledges that Chang & Gottlieb do not teach a composition comprising GAD in a pharmaceutically acceptable carrier for human use. However, the Examiner says that it would have been obvious to modify Chang & Gottlieb's composition in view of the fact that Chang & Gottlieb teach a carrier suitable for use in rats, and that carriers suitable for use in humans were known. This rejection is respectfully traversed.

The motivation that led Chang & Gottlieb to combine GAD with a carrier suitable for administration to rats would not have led one to combine GAD with a carrier for administration to humans. Chang & Gottlieb's motivation was to use their composition for inoculation of rats and thereby generate monoclonal antibodies to GAD useful for research purposes. Procedures for generating monoclonal autoantibodies at minimum expose the animal to a risk of undesired immune responses, and typically involve killing the animal. Such procedures are possible in laboratory animals only because the animals are deemed expendable. However, it is not acceptable to expose a human to such risks simply for the purpose of producing a monoclonal antibody for research purposes. Further, one would not have been motivated to replace Chang & Gottlieb's complete Freund's adjuvant with a carrier suitable for human administration if the resulting composition were simply going to be administered to a laboratory animal. Complete Freund's adjuvant is the most commonly used adjuvant for inducing an immune response in laboratory animals on account of the strong and prolonged response induced (see Harlow & Lane, *Antibodies: A Laboratory Manual* (CSH, 1988 at p. 98). In general, carriers suitable for use in humans would be expected to be less effective and offer no compensating advantages for use in laboratory animals, so the skilled person would not use them. Thus, Chang & Gottlieb's motivation of producing a monoclonal antibody for research purposes would not have led one to combine GAD with a carrier suitable for human administration.

The only motivation that would in fact have led one to combine GAD with a carrier suitable for human administration is the realization that GAD has a therapeutic benefit for humans. Such is disclosed by the present application and not by the prior art. For these reasons, claims 35 and 54-57 were not obvious and the rejection should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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